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Factors associated with early seizures after surgery of unruptured intracranial aneurysms

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ABSTRACT

Objective: The aim of the study was to better define the incidence of and risk factors for early seizures after repair of unruptured intracranial aneurysms in modern microsurgical techniques.
Patients and methods: The medical records of 414 consecutive patients who underwent neck clipping of unruptured intracranial aneurysms in our institution over a 5-year period were retrospectively reviewed. Clinical and neuroimaging variables were analyzed to investigate putative predictors of perioperative seizures using multivariate logistic regression analysis.
Results: Overall, 24 patients (5.8%) developed seizures within 14 days of surgery without routine prophylactic use of anticonvulsants. Eleven patients experienced partial seizures, while 13 experienced secondary generalized seizures. The interval between surgery and seizure onset was less than 6 h in 8 patients, 6–24 h in 3, and 1–14 days in 11. History of dialysis (odds ratio [OR] = 77.6, 95% confidence interval [CI] 7.5–1783.4, $P < 0.001$), and presence of cerebral contusion (OR = 5.1, 95% CI 1.3–16.9, $P = 0.02$) or infarction (OR = 13.9, 95% CI 3.9–48.5, $P < 0.001$) detected by postoperative computed tomography were independent and significant risk factors. No patients with early seizures went on to develop refractory epilepsy.
Conclusions: Dialysis and iatrogenic brain damage were associated with a higher risk of early seizures after aneurysm surgery. Our data support the selective use of anticonvulsants during the perioperative period of elective aneurysm surgery.

1. Introduction

Postoperative seizures are a rare but established complication of intracranial aneurysm surgery. In particular, in the prophylactic repair of unruptured aneurysms, the decline in the functional quality of life due to epilepsy is a significant problem. The reported incidence, however, varies between 2.6% and 15.7%, reflecting differences in clinical practice among surgeons and institutions [1–8]. Recently, several authors advocated the contraindication of prophylactic anticonvulsants because of the low incidence of seizures in modern microsurgical techniques without cortical resection [1,6,9]. On the other hand, the specific patient/lesion characteristics associated with postoperative epilepsy remain to be elucidated. The objective of this study was to identify the independent predictors of seizures after surgical repair of unruptured aneurysms with current surgical standards.

2. Patients and methods

2.1. Study population

The medical records of consecutive patients with unruptured aneurysms who underwent craniotomy and neck clipping in our institution between April 2008 and December 2013, with at least 3 years of follow-up, were retrospectively reviewed. The diagnosis of the aneurysm was based on 3-dimensional computed tomography (CT) angiography or digital subtraction angiography. The indication of surgery was based on the Japanese Guidelines for the Management of Stroke 2009 [10]. We obtained the following parameters from all patients: age,

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sex, clinical history of hypertension, diabetes mellitus, hyperlipidemia, dialysis, seizures, smoking status, and routine laboratory test including glutamic-oxaloacetic/pyruvic transaminases, blood urea nitrogen/creatinine, number, size, and location of the aneurysm, operating time, craniotomy side, preoperative and postoperative neurological deficits, and postoperative hemorrhagic/ischemic complications. Patients with a previous history of subarachnoid hemorrhage or other hemorrhagic stroke and those who had undergone craniotomy were excluded from this study. Three months after surgery, outcomes were evaluated using the modified Rankin scale (mRS).

2.2. Patient management

Preoperative and postoperative prophylactic use of anticonvulsant was not provided routinely in patients without a history of seizures, while the same prescribed regimen of anticonvulsants was continued for those who had been on medication for epilepsy. Diazepam was administered immediately to patients who developed postoperative seizures, and oral anticonvulsants were given subsequently. The diagnosis of seizure was obtained symptomatologically and an electroencephalogram was not routinely performed. Epilepsy was defined as at least two unprovoked or reflex seizures > 24 h apart [11]. Brain CT scans were obtained immediately and one day after the operation, while magnetic resonance imaging/angiography (MRI/A) was performed 2–4 weeks later to evaluate surgical complications.

2.3. Statistical analyses

Univariate analysis comparing variables among patients with and without postoperative early seizures was performed with the Fisher's exact test and the Mann-Whitney U test. Factors significantly associated with seizures were investigated with multivariate logistic regression analysis. P-values less than 0.05 were considered significant. All analyses were performed with the commercially available software SPSS (version 23; IBM Corp, Armonk, New York, USA).

2.4. Ethics committee approval

The requirement for informed consent was waived due to the retrospective nature of the study. The Institutional Review Board of Saitama Medical University International Medical Center approved all aspects of this study (application number 13–183).

3. Results

3.1. Demographics and characteristics

Overall, 414 patients with unruptured aneurysms, 139 males (33.6%) and 275 females (66.4%), aged from 18 to 84 years (median 63 years, interquartile range 59–70 years), were surgically treated during the 5-year period. Among them, 265 (64.1%) had a clinical history of hypertension, 54 (13.0%) had diabetes mellitus, 146 (35.5%) had hyperlipidemia, and 153 (40.0%) were current smokers. Preoperative blood analysis revealed liver dysfunction in 16 (3.9%), and renal dysfunction in 35 (8.5%) of the patients, regardless of symptoms. Only 7 patients (1.7%) had epilepsy and received anticonvulsant medication preoperatively, and 4 patients (1.0%) were receiving hemodialysis before surgery.

Among the patients, 282 (68.1%) had a single aneurysm, and 132 (31.9%) had multiple aneurysms. The aneurysms were asymptomatic in 391 patients (94.4%), and symptomatic in 23 (5.6%), causing mass effect to the surrounding structures or distal embolism. The median aneurysm size was 5.1 mm (interquartile range 4.2–7.0 mm). A total of 414 craniotomies were performed to treat 475 aneurysms. The aneurysms were clipped via the right transsylvian route in 208, left transsylvian route in 161, and interhemispheric route in 45 patients. The median operation time was 270 min (interquartile range 224–340 min).

Table 1
Demographic and clinical characteristics of the patients, MCA: middle cerebral artery; ACA: anterior cerebral artery; IC: internal cerebral artery.

Variables Patient characteristic	Cases Number (%) or median (interquartile range)
Male	139 (33.6)
Female	275 (66.4)
age (years)	63 (59-70)
hypertension	265 (64.1)
Smoking	153 (40.0)
Diabetes	54 (13.0)
hyperlipidemia	146 (35.5)
liver dysfunction	16 (3.9)
renal dysfunction	35 (8.5)
Dialysis	4 (1.0)
preoperative seizures	7 (1.7)
Aneurysm	
Single	282 (68.1)
Multiple	132 (31.9)
MCA	203 (42.7)
ACA	135 (28.4)
ICA	131 (27.6)
Posterior circulation	6 (1.3)
Size (mm)	5.1 (4.2-7.0)
Surgical approach	
right pterional	208 (50.2)
left pterional	161 (38.9)
interhemispheric	45 (10.9)
operation time (min)	270 (224-340)
Hospitalization (day)	13 (11-17)

Postoperatively, contusional, ischemic, hemorrhagic, and infectious surgical complication were detected by CT or MRI in 30 (7.3%), 29 (7.0%), 28 (6.8%), and 12 (2.9%) patients, respectively, and were symptomatic in 36 patients (8.7%). The median hospitalization was 13 days (interquartile range 11–17 days). All patients were followed in our clinic routinely. Three months after surgery good outcome (mRS 0–2) was obtained in 97.1% (397/409) of the patients, while 5 patients were lost to follow up. Clinical and demographic characteristics of the patients are summarized in Table 1.

3.2. Incidence and severity of early postoperative seizures

The overall incidence of postoperative early seizures was 5.8% (24/414), including only one patient with a clinical history of epilepsy. Fifteen patients sustained one seizure, while 9 had two or more. The seizure type was partial in 11 patients and generalized in 13, including 3 patients who developed status epilepticus and needed intensive care including sedation and respiratory support. The timing of the first postoperative seizure was within 6 h of surgery in 8 patients, 6–24 h in 3, 1–3 days in 4, and 4–14 days in 9 patients. All these patients subsequently received oral anticonvulsants, and the seizures were temporary in all cases. No patient developed intractable epilepsy, and anticonvulsants were successfully discontinued at the last follow up in 7 patients without recurrence.

3.3. Risk factors of postoperative early seizures

Univariate analysis revealed that dialysis, hypertension, postoperative infarction, hemorrhage, contusion, and hospitalization were significantly different between patients with or without postoperative seizures, while other factors showed no significant differences (Table 2). Among the significant factors, hospitalization was in some cases due to postoperative seizures. The patients that developed status epilepticus needed intensive care, including sedation and respiratory support, and thus required longer hospitalization for treatment and for rehabilitation to recover from disuse atrophy. Additionally, patients

Table 2
Comparison of variables between patients with and without seizures. Continuous variables are expressed as median (interquartile range), and the P-value is computed with the Mann-Whitney U test. Categorical variables are expressed as number (percentage) and the P value is computed with the Fisher's exact test. HT: hypertension; DM: diabetes mellitus; MCA: middle cerebral artery.

Variables	seizure (+)	seizure (-)	P-value
Age (years)	64 (59–68)	64 (59–70)	0.97
Female	15 (62.5)	260 (66.7)	0.66
Past history			
HT	20 (83.3)	245 (62.8)	0.04
DM	4 (16.7)	50 (12.8)	0.54
hyperlipidemia	9 (37.5)	137 (35.1)	0.83
liver dysfunction	0 (0)	(4.1)	0.61
renal dysfunction	3 (12.5)	32 (8.2)	0.44
dialysis	3 (12.5)	1 (0.3)	< 0.001
smoking	11 (45.8)	142 (36.4)	0.39
seizure history	1 (4.2)	6 (1.5)	0.34
Aneurysm			
single	19 (79.2)	263 (67.4)	0.27
Size (mm)	5.8 (3.9–7.0)	5.1 (4.0–7.3)	0.98
MCA	9 (32.1)	164 (36.7)	0.66
non-MCA	19 (67.9)	283 (63.3)	
Surgical approach			
right pterional	13 (54.1)	195 (50)	0.95
left pterional	9 (37.5)	152 (39)	
interhemispheric	2 (8.4)	43 (11)	
Operation time (min)	289 (252–401)	268 (224–339)	0.16
Surgical complication			
contusion	5 (20.8)	25 (6.4)	0.02
hemorrhage	5 (20.8)	23 (5.9)	0.02
infarction	7 (29.2)	22 (5.6)	< 0.001
infection	1 (4.2)	11 (2.8)	0.52
Hospitalization (day)	18 (14–40)	13 (11–16)	< 0.001

Table 3
Multivariate logistic regression.

Variables	Adjusted Odds Ratio	95% CI	P–value
postoperative contusion	5.08	1.31–16.86	0.02
postoperative hemorrhage	2.86	0.71–9.70	0.13
postoperative infarction	13.88	3.93–48.48	< 0.001
hypertension	1.69	0.55–6.33	0.37
dialysis	77.6	7.47–1783	< 0.001

needing anticonvulsant medication required several days of additional hospitalization to check the side effects of those drugs. For these reasons, hospitalization as a risk factor was excluded from further analysis. Postoperative contusion, infarction and dialysis were found to be independent significant predictors of postoperative seizures by multivariate logistic regression analysis (Table 3).

4. Discussion

In the prophylactic repair for patients with unruptured aneurysms, the benefit of the treatment depends on weighing the risk of sustaining aneurysmal subarachnoid hemorrhage (SAH) from an untreated aneurysm against that of developing perioperative complications. In this context, postoperative seizure is a serious complication significantly decreasing the patient's quality of life after surgery.

In the past, only 8 studies reported the frequency of early seizures after clipping of unruptured aneurysms [1–8], the frequency of postoperative seizures ranging from 2.6 to 15.7%, and preoperative seizure history and surgical complications were reported to be risk factors for early seizure. The present study revealed that dialysis patients, postoperative cerebral contusion and infarction are risk factors for postoperative early seizure. Although there is no report claiming a significant association of neck clipping of unruptured cerebral aneurysms in dialysis patients and epileptic convulsions, several authors reported that patients under dialysis encountered significantly higher postoperative complications and mortality than controls even in non-brain surgery, and dialysis often causes epileptic seizures regardless of surgery [10,12–23].

Importantly, all cases of seizures in our study turned out to be temporary, including the three patients that developed status epilepticus. This is in agreement with a study on stroke patients [24], which reported that early seizures (within 2 weeks from stroke onset) were not associated with a high risk of developing epilepsy.

In a previous study of surgery for ruptured aneurysm, brain damage was found to be a risk factor for postoperative seizure, whether brain damage was caused by SAH or iatrogenically [25,26]. In the case of unruptured aneurysms, this study demonstrates that iatrogenic brain lesions – cerebral contusions and infarctions – may also be significant risk factors for postoperative early seizure. In theory, given that an aneurysm neck is located in the subarachnoid space, microsurgical repair should be possible without significant brain damage, although it is difficult to avoid the potential risk of seizure in practice [8]. Surgeons must reflect on their surgical skills, gain an appropriate amount of experience, and pay special attention to the efforts needed to avoid or limit iatrogenic brain damage.

Recent studies do not recommend the routine use of antiepileptic drugs for the prevention of postoperative seizures after clipping [1,6,9]. In our institution, we do not use postoperative anticonvulsant prophylaxis for patients treated for unruptured cerebral aneurysms at present. However, in the future, we may be able to decrease the incidence of postoperative seizures by the use of anticonvulsant prophylaxis, limited to patients in dialysis and those who had brain damage during surgery.

Our study has several limitations. First, it is a single-center retrospective study, and the patients included might reflect some selection and referral biases inherent in a territory care practice at an academic medical center. Second, only 4 patients were under dialysis out of the 414 patients surgically treated for unruptured aneurysm repair in this study, although 3 of them developed a postoperative seizure. In the future, more dialysis patients will go through neck clipping, and we will be able to assess the association between dialysis and seizures on a larger sample size.

5. Conclusions

This study revealed that dialysis, postoperative cerebral contusion, and infarction are risk factors for early seizures after surgery of unruptured intracranial aneurysms. The selective use of anticonvulsants during the perioperative period of elective aneurysm surgery for high risk patients may reduce the risk of postoperative early seizures.

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Declarations of interest

None.

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